

Question 2

Is there a specific strain, or isolate of virus(es) that should be used in animal studies and what challenge dose should be used if the goal is to protect against a potential bioterrorist release?

Is there a specific strain, or isolate of virus(es) that should be used in animal studies and what challenge dose should be used if the goal is to protect against a potential bioterrorist release?

STRAIN

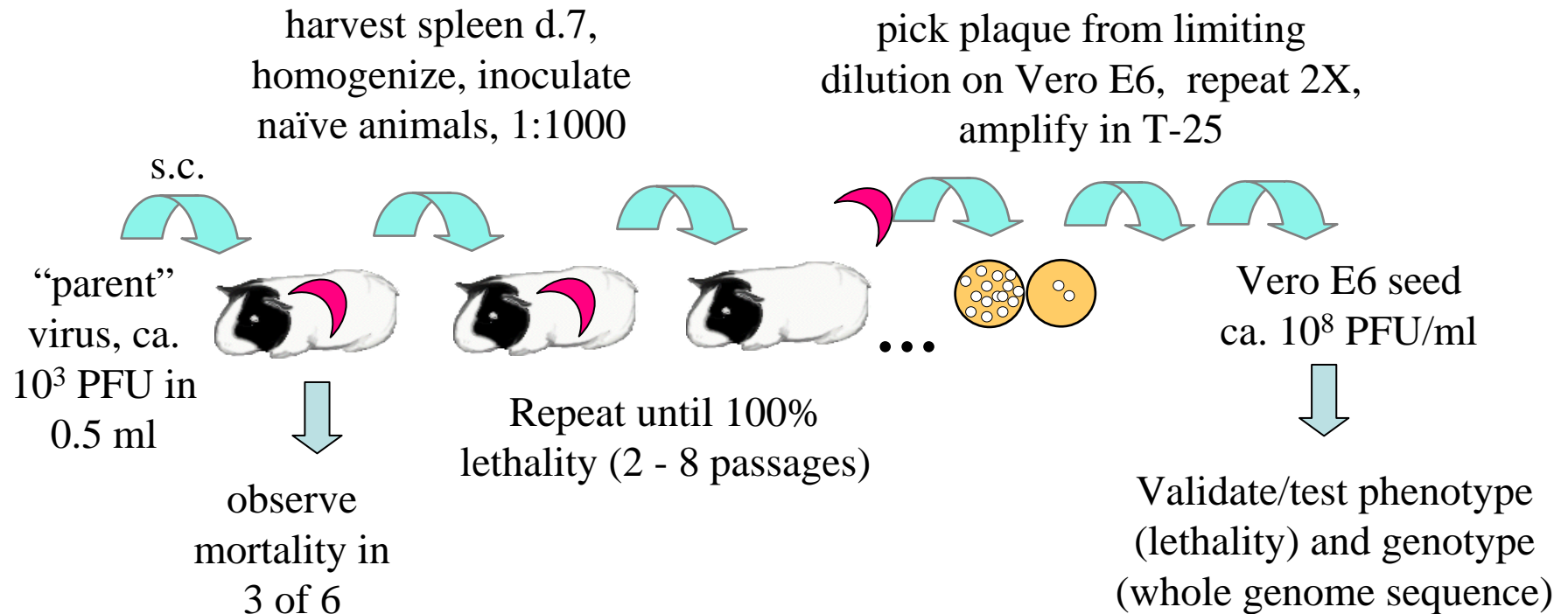
1. Let us begin by presupposing that most groups of investigators already considered these questions carefully, so we may be guided in part by what has been done. Look at the published literature.
2. Standardization will provide results that are more consistent and comparable among laboratories, and will minimize the possibility of artifacts (e.g. contamination, drifts in virulence) ...
3. However, choice of strain in terms of RELEVANCE remains to a large degree a “known unknown.” Threat from nature or “evildoers” is unpredictable. If any strain happens to be uniquely potent in terms of evoking broad immunity, it has not yet been shown.
4. Without exception thus far (?), filoviruses from human cases are almost uniformly lethal for nonhuman primates; for lethality in rodents, viruses must be adapted by repeated passage and selection.

Is there a specific strain, or isolate of virus(es) that should be used in animal studies and what challenge dose should be used if the goal is to protect against a potential bioterrorist release?

STRAINS: The Special Case of Rodent-adapted Filoviruses

1. Genotypic changes associated with increased rodent virulence are not the same in different rodent-adapted viruses.
2. Guinea pig-adapted viruses are generally not virulent for mice.
3. Paucity of data on whether rodent adaptation diminishes virulence for NHP (has not been a priority use of NHP).
4. Most of the rodent-adapted viruses have been subjected to 3X plaque purification. This isn't necessarily a bad thing, but different from typical NHP challenge seeds.
5. Not all viruses have been adapted successfully to cause lethal disease in rodents; guinea pigs typically easier than mice.

Derivation of Guinea pig Adapted and Plaque-picked Marburg Viruses



Hevey M, Negley D, Geisbert J, Jahrling P, Schmaljohn A. Antigenicity and vaccine potential of Marburg virus glycoprotein expressed by baculovirus recombinants. *Virology* 1997;239:206-216.

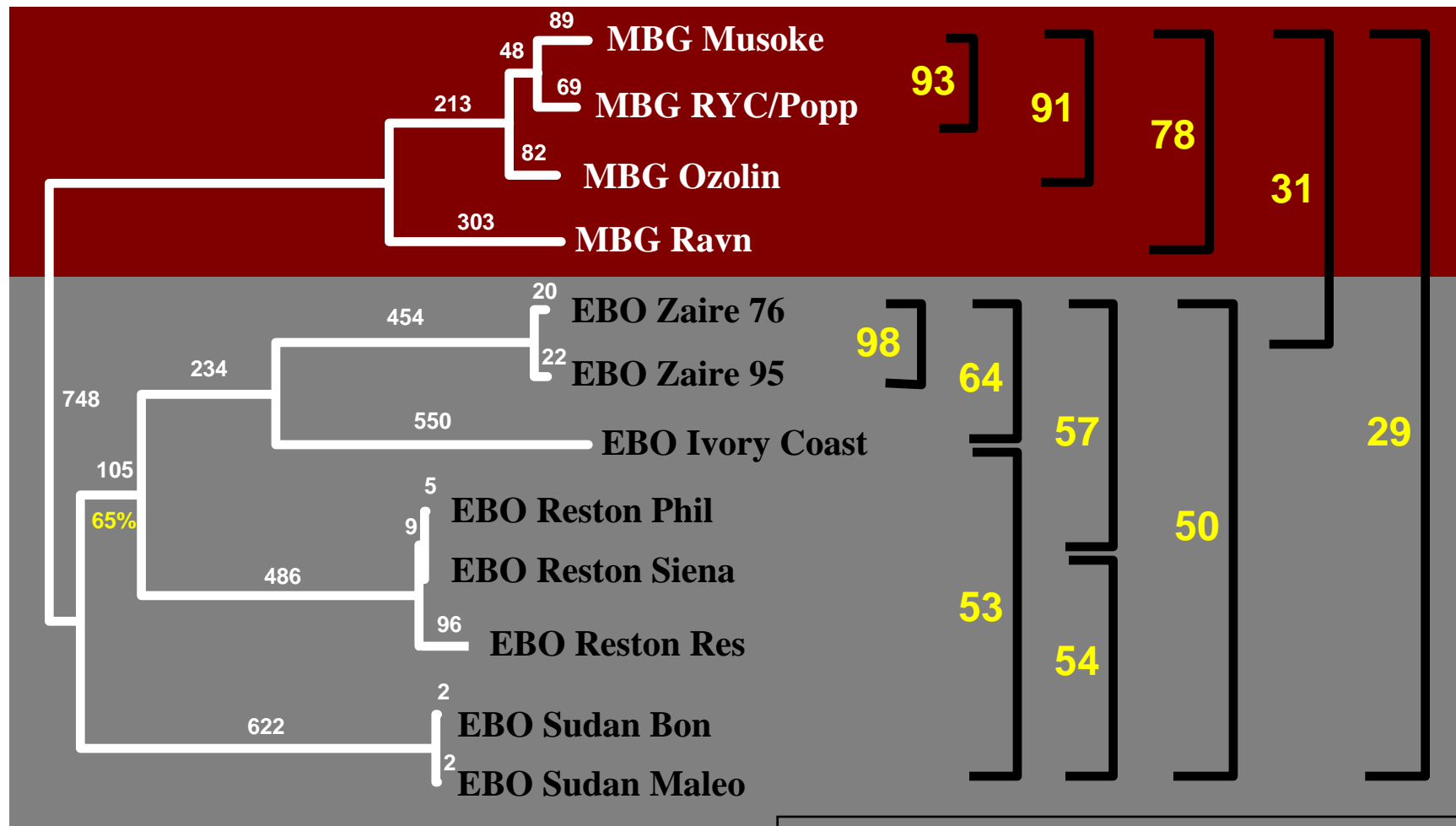
Lofts, L., Ibrahim, M.S., Negley, D., Hevey, M.C., and Schmaljohn, A.L. (2007). Genomic differences between guinea pig lethal and non-lethal Marburgvirus variants. *Journal of Infectious Diseases*

Diversity among Filoviruses

Phylogenetic Relationships
from glycoprotein gene sequence

VIRUS, Isolate

Amino Acid Identity (%)*



Approximations from BLASTP pairwise comparisons of translated glycoprotein genes

Is there a specific strain, or isolate of virus(es) that should be used in animal studies and what challenge dose should be used if the goal is to protect against a potential bioterrorist release?

DOSE

1. Again, let us begin by presupposing that most groups of investigators already considered these questions carefully, so we may be guided in part by what has been done. Look at the published literature.
2. Most studies to date have used 100 - 1,000 PFU (\approx LD₅₀) under the following logic: a) this is a relevant dose for fomite/needlestick and easily achievable in aerosol; b) this moderate dose results in less variability in time to death of NHP compared with very low doses; c) reducing challenge dose to 1 - 10 LD₅₀ is unhelpful both in terms of relevance and the practicality of measuring the dose delivered; d) very low dose (i.e. few virions, even if >10 LD₅₀) can make it difficult to differentiate “sterile immunity” from “missed”

